

### REMARKS

Applicants have amended claims 1, 3-5, 8-9, 12-14, 16, 20-22, 24, 27-28, and 30-31 to correct informalities and more clearly delineate the claimed subject matter. Support for the recitation "for submerged culture" in claims 1, 13 and 21 can be found, for example, at page 3, lines 17-22 of the specification. Support for the recitations "a nutritional solid substrate that receives said filamentous fungi" in claim 1 and "a grain particle that receives said *Monascus* species" in claims 13 and 21 can be found, for example, in the paragraph bridging pages 5-6 of the specification.<sup>1</sup> Support for the term "nutritional" recited in claims 1, 3, 8, and 12 can be found, for example, at page 5, line 26. Support for the term "grain" recited in claims 4 and 5 can be found, for example, at page 6, lines 1-11 of the specification.

At the Examiner's suggestion, Applicants have changed the dependency of claims 4 and 27, which now depend from amended claims 3 and 21, respectively. Applicants have also changed the dependency of claim 9, which now depends from amended claim 1, and cancelled claim 29 to eliminate claim duplicity.

Finally, Applicants have also corrected typographical errors in claims 5, 14, and 22 and in the paragraph beginning at page 5, line 26 of the specification.

Claims 1-28 and 30-31 are now pending. Reconsideration of the application, as amended, is requested in view of the following remarks:

#### Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-31 were rejected by the Examiner for lack of a written description. More specifically, the Examiner stated that there was no adequate support for the term "full" as in the limitation "full-grain particle" recited in claims 1, 3, 8, 12-14, 16, 20-22, 24, and 28. See the Office Action, page 3, lines 1-2. Note that Applicants have cancelled claim 29.

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<sup>1</sup> As disclosed in this passage of the specification, a solid substrate or grain particle provides a place where filamentous fungi or the *Monascus* species can attach to. With this teaching, one skilled in the art would clearly recognize that the solid substrate or grain particle provides a place that receives filamentous fungi, such as the *Monascus* species. Thus, the specification sufficiently supports these newly added limitations.

Note that a claim does not have to be set forth verbatim in the specification. In *In re Wright*, 9 USPQ2d 1649 (Fed. Cir. 1989), the Federal Circuit, in reversing a Board's 35 U.S.C. § 112, first paragraph rejection, held that there was adequate written description support for applicant's claim limitation, despite the fact that it was not set forth "*in haec verba*" (i.e., "in these words" or "verbatim") in the specification.

To overcome this rejection, Applicants have amended these claims to delete the limitation "full-grain particle" from claims 1, 3, 8, and 12 and the term "full-" from claims 13-14, 16, 20-22, 24, and 28, and request withdrawn of this rejection.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-31 on one or two grounds. Applicants submit that the above amendment has overcome the rejection.

Note that the Examiner further rejected claims 13, 21, and their dependent claims as being indefinite. It is the Examiner's position that the claims do not set forth any steps involved in "the use" of a grain particle solid grain substrate. See the Office Action, the paragraph bridging pages 3-4. For a complete the record, Applicants would like to point out that rejected claims 13 and 21 include two steps: (a) preparing a medium comprising a full-grain particle solid grain substrate, and (b) inoculating the medium with the *Monascus* species in a bioreactor wherein the mycelia of the *Monascus* species attached to the full-grain particle solid grain substrate. In other words, the substrate is used both as a source for nutrients and as a matrix for cell attachment. Thus, the recitation of steps (a) and (b) clearly points out the use of the substrate. For this reason, the claims are definite. So are their dependent claims, which inherently include both steps (a) and (b). In the sole interest of moving this case toward allowance, Applicants have amended claims 13 and 21 to delete the recitations "by using a full-grain particle solid substrate" and "by using a full-grain particle solid grain substrate," respectively.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1-31 as being anticipated by U.S. Patent No. 5,013, 655 to Bayer et al. ("Bayer"). Applicants respectfully traverse and will discuss independent claims 1, 13, and 21 first.

Amended claim 1 is drawn to a method for cultivating filamentous fungi. The method includes (a) preparing a medium for submerged culture comprising a nutritional solid substrate that receives the filamentous fungi; and (b) inoculating the medium with the filamentous fungi in a bioreactor to carry out fermentation wherein said filamentous fungi are attached to the

nutritional solid substrate. In other words, the method requires suspending a solid substrate (e.g., a grain particle) in a liquid medium (e.g., water and broth, see page 9, lines 17-19 and page 11, lines 7-10) for submerged culture and cultivating filamentous fungi on the solid substrate suspended in the liquid medium.

Bayer does not teach or suggest preparing or inoculating a medium for submerged culture. Rather, it teaches growing a microorganism of the genus *Monascus* in reactors on solid rice that is not suspended in a liquid medium. See column 2, lines 47-51. Thus, Bayer does not anticipate claim 1, as amended.

Amended claim 13 covers a method for cultivating the *Monascus* species and amended claim 21 covers a method for producing metabolites from a cultivation of the *Monascus* species. Both methods include the steps of preparing a medium for submerged culture and inoculating the medium with the *Monascus* species to carry out fermentation. For the same reasons set forth above, they are not anticipated by Bayer.

As amended 1, 13, and 21 are not anticipated by Bayer, neither are claims 2-12, 14-20, 22-28, and 30-31, which directly or indirectly depend from them.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected all pending claims for obvious on one or more grounds. Applicants will address each of the grounds.

I

Claims 1-4, 6, 13, 21, and 29-31 were rejected as being unpatentable over Bayer in view of U.S. Patent No. 4,954,440 to Johal et al. ("Johal"). See the Office Action, page 3, lines 12-15. Applicants respectfully traverse.

Among the rejected claims, claims 1, 13, and 21 are independent. They are drawn to a method for cultivating filamentous fungi, a method for cultivating the *Monascus* species, and a method for producing metabolites from cultivation of the *Monascus* species, respectively. All three methods include the step of preparing a medium for submerged culture, which includes a solid substrate or a grain particle that is suspended in a liquid. The methods further include the step of inoculating the medium with filamentous fungi or the *Monascus* species.

As noted above, Bayer does not suggest preparing or inoculating a medium for submerged culture. Further, it explicitly teaches "culturing a microorganism of the genus the *Monascus* in a sterilizable fluidized-bed fermenter of low water content." See the abstract. In fact, the microorganism in the fermenter was "moistened (i.e., slightly wet)." See column 3, lines 18-20. To the extent that the microorganism was moistened and the fermenter was of low water content, Bayer teaches away from amended claims 1, 13, and 21, all of which require preparing or inoculating a liquid medium for submerged culture.

Johal, as pointed out by the Examiner, teaches that a medium for culturing filamentous fungi contains assimilable carbon and nitrogen sources, organic materials and minor organic and inorganic nutrients such as trace salts, trace elements, vitamins, amino acids and the like. See column 4, lines 29-35. Further, it teaches "a process to recover polysaccharides... from filamentous fungi wherein the fungi adhere to the surface of porous, non-particulate, inert, fixed support in an immobilized cell bioreactor..." See column 2, lines 20-29. Also, the support is "chemically and/or biological inert under conditions of use (column 3, lines 60-61)." In other words, it is not a nutritional source for the fungi. Thus, Johal also teaches away from amended claims 1, 13, and 21, which require a nutritional solid substrate suspended in a liquid.

For the above reasons, Bayer and Johal, alone or combined, do not render amended claims 1, 13, and 21 obvious. As these claims are non-obvious, so are claims 2-4, 6, 28, and 30-31, which directly or indirectly depend from them.

## II

The Examiner rejected claims 1-5, 7-8, 13-16, 21-23, and 29-31 as being unpatentable over U.S. Patent No. 4,031,250 to Hass et al. ("Hass") alone. See the Office Action, page 6, last paragraph through page 8, penultimate paragraph. Applicants disagree and will discuss independent claims 1, 13, and 21 first.

As mentioned in Part I above, amended claims 1, 13, and 21 are drawn to methods that include two steps of preparing a medium for submerged culture and inoculating the medium with filamentous fungi or the *Monascus* species.

Hass teaches a method for producing pigments by growing the *Monascus purpureus* on rice or corn. The method includes culturing the *Monascus purpureus* on agar slant, washing the

slant with water, and inoculating the *Monascus purpureus* into sterilized rice or corn. According to the Examiner, it is obvious to grind, crush, and flake rice and to use husked corn and cooked rice for practicing the methods of Hass. Note that Hass points out that:

A critical parameter in the inoculation process is the moisture present in the rice or corn/mold mixture. The preferred condition is to have water present in an amount sufficient to keep the rice or corn moist to the eye but not such that free excess water is apparent. Excess water has the effect of facilitating the growth of other molds and even bacteria, a particularly undesirable result (see column 2, lines 17-24).

To the extent that Hass states that "[t]he preferred condition is ... to keep the rice or corn moist" and that "[e]xcess water [facilitates] a[n] undesirable result," it teaches away from amended claims 1, 13, and 21, which require preparing or inoculating a liquid medium for submerged culture.

The Examiner further rejected the claims over Hass in view of Johal and US patent 3,765,906 to Yamaguchi ("Yamaguchi"). See the Office Action, page 8, second paragraph.

Johal and Yamaguchi both teach culturing the *Monascus* species in bioreactors. As set forth in Part I above, Johal teaches a non-nutritional solid support for the fungi. As noted in Applicants' previous response dated April 18, 2002, Yamaguchi teaches a medium that does not contain solid support.

Thus, Hass, Johal, and Yamaguchi, alone or combined, again, do not suggest amended claims 1, 13, and 21 and their dependent, claims 2-5, 7, 8, 14-16, 22, 23, 30, and 31.

### III

The Examiner further rejected claims 1-4, 7-10, 13, 15-17, 21, 23-26, and 29-31 as being obvious over Hass in view of Bayer and Tung et al., *Bioprocess Engineering*, 1997, Vol. 17, No.1 pp1-5 ("Tung"). See the Office Action, page 8, last two lines.

Tung teaches a fermentation method including using airlift reactors. It does not suggest the step of preparing a medium for submerged culture or the step of inoculating the medium with filamentous fungi or the *Monascus* species, as recited in claims 1, 13, and 21. Further, as noted in Parts I and II above, both Hass and Bayer teach away from amended claims 1, 13, and 21.

Thus, Hass, Bayer, and Tung, alone or combined, do not render amended claims 1, 13, and 21 obvious. As these claims are non-obvious, so are claims 2-4, 7-10, 15-17, 23-26, 30, and 31, which directly or indirectly depend from them.

#### IV

The Examiner finally rejected claims 1-4, 6, 11-13, 19-21, and 27-31 as being obvious over Hass in view of Johal. See the Office Action, page 11, lines 7-8. Applicants disagree.

As noted in Parts I and II above, Hass and Johal teach away from amended claims 1, 13, and 21. Thus, these claims and their dependent claims are non-obvious.

#### CONCLUSION

Applicants submit that the grounds for rejections asserted by the Examiner have been overcome, and the claims, as pending, define subject matter that is novel, non-obvious, definite, and in compliance with the written description requirement. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Attached is a marked-up version of the changes being made by the current amendment.

Enclosed is a \$465 check for the Petition for Three-Month Extension of Time fee. Please apply any other charges to Deposit Account No. 06-1050, reference Attorney Docket No. 08415-003001.

Respectfully submitted,

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Y. Rocky Tsao  
Y. Rocky Tsao  
Attorney for Applicants  
Reg. No. 34,053



PTO Customer No: 26161

**Version with markings to show changes made**

In the specification:

Paragraph beginning at page 5, line 26 has been amended as follows:

The term "nutritional [nutritionally] solid substrate [substrates]" used herein is defined as a substrate which keeps its solid morphology in medium to provide a place where the mycelia can attach to, and to provide a carbon source required for the growth of the fungi. The carbon source can be, for example, carbohydrates. Suitable carbohydrates include [carbohydrate includes], but are not limited to, rice, wheat and other grains. Prior to adding to the medium, the grain may be treated by the process of husking, cooking[cocking] and sterilizing. Because the structure of the grain (e.g. rice or wheat) is very suitable for mycelia attachment, and grain can provide the major nutrition source for the fungi, the cultivation of the *Monascus* species of the present invention is carried out by using a medium comprising suspended nutritional [nutritionally] solid substrate such as rice substrates, so that it can possess both the properties of mycelia attachment and suspended fluidity.

In the claims:

Claim 29 has been cancelled.

Claims 1, 3-5, 8, 9, 12-14, 16, 20-22, 24, 27, 28, 30, and 31 have been amended as follows:

1. (Once amended) A method for cultivation of filamentous fungi comprising the steps of:
  - (a) preparing a medium for submerged culture comprising a nutritional [nutritionally full-grain particle]solid substrate that receives said filamentous fungi; and
  - (b) inoculating said medium with said filamentous fungi in a bioreactor to carry out fermentation wherein the mycelia of said filamentous fungi are attached to said nutritional [nutritionally full-grain particle]solid substrate.

3. (Once amended) The method as claimed in claim 1, wherein said nutritional [nutritionally full-grain particle] solid substrate is a carbohydrate.

4. (Once amended) The method as claimed in claim 3[1], wherein said carbohydrate is grain [rice].

5. (Once amended) The method as claimed in claim 4, further comprising the steps of husking, cooking [cocking] and sterilizing said grain [rice] before adding to said medium.

8. (Once amended) The method as claimed in claim 7, wherein the culturing comprises:

- (1) inoculating said filamentous fungi from a stock culture to a new agar plate and incubating in an incubator for 5 to 7 days;
- (2) washing spores and mycelia grown on said plate with sterile water; and
- (3) cultivating for about 36 to 48 hours said spores and mycelia in a medium comprising a nutritional [nutritionally full-grain particle] solid substrate by shaking to form a culture.

9. (Once amended) The method as claimed in claim 1 [8], wherein said bioreactor is a pneumatic bioreactor.

12. (Once amended) The method as claimed in claim 11, wherein the medium of the batch comprises a nitrogen source and a nutritional [nutritionally full-grain particle] solid substrate.

13. (Once amended) A method for cultivation of the *Monascus* species [by using a full-grain particle solid substrate] comprising the steps of:

- (a) preparing a medium for submerged culture comprising a [full-] grain particle [solid grain substrate] that receives said *Monascus* species; and



(b) inoculating said medium with said *Monascus* species in a bioreactor to carry out fermentation wherein the mycelia of said *Monascus* species are attached to said [full-] grain particle [solid grain substrate].

14. (Once amended) The method as claimed in claim 13, further comprising the steps of husking, cooking [cocking] and sterilizing said [full-]grain particle [solid grain] before adding to said medium.

16. (Once amended) The method as claimed in claim 15, wherein the culturing comprises:

- (1) inoculating said *Monascus* species from a stock culture to a new agar plate and incubating in an incubator for 5 to 7 days;
- (2) washing spores and mycelia grown on said plate with sterile water; and
- (3) cultivating for about 36 to 48 hours said spores and mycelia in a medium comprising a [full-]grain particle [solid substrate] by shaking,[,] to form a culture.

20. (Once amended) The method as claimed in claim 19, wherein the medium of the batch comprises a nitrogen source and a [full-]grain particle [solid grain substrate].

21. (Once amended) A method for producing metabolites from [the] cultivation of the *Monascus* species [by using a full-grain particle solid grain substrate] comprising the steps of:

- (a) preparing a medium for submerged culture comprising a [full-]grain particle [solid grain substrate] that receives said *Monascus* species; and
- (b) inoculating said medium with said *Monascus* species in a bioreactor to carry out fermentation wherein the mycelia of said *Monascus* species are attached to said [full-]grain particle [solid substrate].

22. (Once amended) The method as claimed in claim 21, further comprising the steps of husking, cooking [cocking] and sterilizing said [full-]grain particle [solid grain substrate] before adding to said medium.

24. (Once amended) The method as claimed in claim 23, wherein the culturing comprises:

- (1) inoculating said *Monascus* species from a stock culture to a new agar plate and incubating in an incubator for 5 to 7 days;
- (2) washing spores and mycelia grown on said plate with sterile water;
- (3) cultivating for about 36 to 48 hours said spores and mycelia in a medium comprising a [full-]grain particle [solid grain substrate] by shaking, to form a culture.

27. (Once amended) The method as claimed in claim 21[20], further comprising cultivating said *Monascus* species using the fed-batch process.

28. (Once amended) The method as claimed in claim 27, wherein the medium of the batch comprises a nitrogen source and a [full-]grain particle [solid grain substrate].

30. (Once amended) The method as claimed in claim 13, wherein the [solid] grain particle [substrate] is rice.

31. (Once amended) The method as claimed in claim 21, wherein the [solid] gain particle [substrate] is rice.